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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Group Art Unit: 1502

Examiner: Gollamudi S. Kishore

In re PATENT REISSUE APPLICATION of:

Patentees : Patrick L. AHL et al.)
U.S. Patent No. : 5,662,930)
Issued : September 2, 1997)
Reissue Application No. : TBD)
Reissue Filed :)
For : REDUCTION OF LIPOSOME-INDUCED)
ADVERSE PHYSIOLOGICAL REACTIONS)
Attorney Docket : 31839-150675)
TLC 201C RIS)

**DECLARATION AND
POWER OF ATTORNEY**

Date:

Honorable Commissioner of Patents and Trademarks
Washington, D.C. 20231

Sir:

We, Patrick L. Ahl, Suresh K. Bhatia, Sharma R. Minchey and Andrew S. Janoff,
DECLARE:

That we are citizens of the United States, India, the United States and the United States,
respectively, and that our post office addresses are, respectively:

Patrick L. Ahl, 2E Brookline Court, Princeton, NJ, 08536, US

Suresh Bhatia, B-165 Sarita Vihar, Mathura Road, New Delhi, 110044, IN

Sharma R. Minchey, 1693 Camp Hill Road, Lafayette, TN, 37083, US

Andrew S. Janoff, 560 Countess Drive, Yardley, PA, 19067, US

That we verily believe ourselves to be the original, first and joint inventors of the invention REDUCTION OF LIPOSOME-INDUCED ADVERSE PHYSIOLOGICAL REACTIONS described and claimed in the United States Letters Patent No. 5,662,930 issued September 2, 1999 on application no. 433,665, filed May 4, 1995;

That we have reviewed and understood the contents of the reissue specification including the claims.

That we acknowledge our duty to disclose information of which we are aware which is material to the examination of this application under Rule 56(a);

We verily believe that the original United States Letters Patent No. 5,662,930, referred to above, is wholly or partly inoperative because the patentees claimed less than they had a right to claim. The specific errors relied upon are the failure to present the following claims:

18. A method of treating an animal with a bioactive agent comprising administering to said animal an anti-inflammatory agent and a liposome composition, wherein said liposome composition induces an adverse physiological reaction in said animal; and reducing said adverse physiological reaction.

19. The method of Claim 18, wherein said adverse physiological reaction is a blood pressure drop.

20. The method of Claim 19, wherein the anti-inflammatory agent is indomethacin.

21. The method of Claim 18, wherein the anti-inflammatory agent is a steroid.

22. The method of Claim 18, wherein the anti-inflammatory agent is non-steroidal.

23. A method of treating an animal with a bioactive agent comprising administering to said animal a composition comprising a liposome and an anti-inflammatory agent, wherein said liposome composition induces an adverse physiological reaction in said animal; and reducing said adverse physiological reaction.

24. A method of treating an animal to reduce adverse physiological reaction in said animal, comprising

administering to said animal a composition comprising a liposome and a bioactive agent;
wherein said liposome composition induces an adverse physiological reaction in said
animal;

administering an anti inflammatory agent, to said animal; and
reducing said adverse physiological reaction.

25. A liposome composition comprising a liposome and a bioactive agent which is an
anti-inflammatory agent.

26. The composition of Claim 25, wherein the anti-inflammatory agent is
indomethacin.

27. The composition of Claim 25, wherein the anti-inflammatory agent is a steroid.

28. The composition of Claim 25, wherein the anti-inflammatory agent is non-
steroidal.

29. A liposome composition comprising a liposome and a bioactive agent which is a
contrast agent, in combination with an anti-inflammatory agent.

30. The composition of Claim 29, wherein the anti-inflammatory agent is
indomethacin.

31. The composition of Claim 29, wherein the anti-inflammatory agent is a steroid.

32. The composition of Claim 29, wherein the anti-inflammatory agent is non-
steroidal.

33. The composition of claim 25, wherein the liposome comprises a lipid bilayer
having a lipid and a surface agent-modified molecule which comprises an anchor and a surface
agent modified molecule, wherein the anti-inflammatory agent is administered to the animal

prior to administration of the liposome composition and wherein the liposome has an average diameter of from at least about 220 nm to about 5000 nm.

34. The composition of claim 25, wherein the liposome has an average diameter of from about 400 nm to about 1000 nm.

35. The composition of claim 25, wherein the liposome is unilamellar.

36. The composition of claim 25, wherein the concentration of surface agent modified molecule in the bilayer is at least about 2 mole percent.

37. The composition of claim 25, wherein the surface modifying agent is a dicarboxylic acid, a monocarboxylic acid or a sulfolipid.

38. The composition of claim 25, wherein the surface modifying agent is a dicarboxylic acid.

39. The composition of claim 38, wherein the dicarboxylic acid is a succinic acid, glutaric acid, adipic acid, bimelic acid, tartaric acid, mucic acid, tetrafluorosuccinic acid, or hexafluoroglutaric acid.

40. The composition of claim 39, wherein the dicarboxylic acid is glutaric acid.

41. The composition of claim 25 wherein the anchor is a phosphatidylethanolamine.

42. The composition of claim 41, wherein phosphatidylethanolamine is dipalmitoyl phosphatidylethanolamine.

43. The composition of claim 25, wherein the surface agent modified molecule comprises a phospholipid anchor having a glycerol anchor and a spacer group and wherein the spacer group comprises a functional group capable of attaching to the glycerol backbone and a functional group capable of attaching to the phosphate group of the phospholipid anchor.

44. The composition of claim 43, wherein the functional group is an hydroxyl, thiol epoxide or amine group.

Moreover, it is believed that the original patent may be wholly or partly invalid by reason of a defective Specification at column 12, line 17. Therein, the term "asteroid" is found; the term is correctly stated as -- a steroid--.

The errors enumerated above arose inadvertently and without fraudulent or deceptive intent on the part of ourselves, the assignee, or our attorneys.

We hereby appoint the following attorneys to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith: Rosanne Goodman (Reg. No. 32,534) and Russell Lindenfeldar (Reg. No. 39,750) at The Liposome Company, Inc., One Research Way, Princeton, New Jersey, 08540, George H. Spencer (Reg. No. 18,038), Norman N. Kunitz (Reg. No. 20,586), Robert J. Frank (Reg. No. 19,112), Gabor J. Keleman (Reg. No. 21,016), Robert Kinberg (Reg. No. 26,925), Jerold I. Schneider (Reg. No. 24, 765), John W. Schneller (Reg. No. 26,031), Suite 1200, 1201 New York Avenue, N.W., Washington, D.C. 20005-3955, Telephone: (202) 962-4800, Telefax: (202) 414-4040. Address all correspondence to VENABLE, P.O. Box 34385, Washington, D.C. 20043-9998.

The undersigned hereby authorize the U.S. attorneys named herein to accept and follow instructions from the undersigned assignee, if any, and/or, if the undersigned is not a resident of the United States, the undersigned's domestic attorney, patent attorney or patent agent, as to any action to be taken in the Patent and Trademark Office regarding this application without direct communication between the U.S. attorneys and the undersigned. In the even of a change in the person(s) from whom instructions may be taken, the U.S. attorneys named herein will be so notified by the undersigned.

The undersigned declare further that all statements made herein of their own knowledge are true and that all statements made on information and belief are believed to be true; and

Further that these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Respectfully submitted,

Date: 11/11/99

By: Patrick L. Ahl

Patrick L. Ahl

Date: Nov. 4, 99

By: Suresh K. Bhatia

Suresh K. Bhatia

Date: _____

By: _____

Sharma R. Minchey

Date: 11/6/99

By: Andrew S. Janoff

Andrew S. Janoff

MVS:rei
DC2-157393

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Applicant or Patentee: The Liposome Company, Inc.
Serial or Patent No.: 09/398,934
Filed or Issued: September 1, 1999
For: REDUCTION OF LIPOSOME-INDUCED ADVERSE
PHYSIOLOGICAL REACTIONS
Attorney's Docket No.: 31839-150675 (TLC 201C RIS)

**VERIFIED STATEMENT (DECLARATION) CLAIMING SMALL ENTITY STATUS
(37 CFR 1.9(d) and 1.27(c) - SMALL BUSINESS CONCERN)**

I hereby declare that I am

- ☐ the owner of the small business concern identified below:
☒ an official of the small business concern empowered to act on behalf of the concern
identified below:

THE LIPOSOME COMPANY, INC.
One Research Way
Princeton Forrestal Center
Princeton, NJ 08540

I hereby declare that the above identified small business concern qualifies as a small business concern as defined in 13 CFR 121.3-18, and reproduced in 37 CFR 1.9(d), for purpose of paying reduced fees under section 41(a) and (b) of Title 35, United States Code, in that the number of employees of the concern, including those of its affiliates, does not exceed 500 persons. For purposes of this statement, (1) the number of employees of the business concern is the average over the previous fiscal year of the concern of the persons employed on a full-time, part-time or temporary basis during each of the pay periods of the fiscal year, and (2) concerns are affiliates of each other when either, directly or indirectly, one concern controls or has the power to control the other, or a third party or parties control or has the power to control both.

I hereby declare that rights under contract or law have been conveyed to and remain with the small business concern identified above with regard to the invention, entitled REDUCTION OF LIPOSOME-INDUCED ADVERSE PHYSIOLOGICAL REACTIONS by inventor(s) Patrick L. Ahl, Suresh Bhatia, Sharma R. Minchey, and Andrew S. Janoff, described in

☐ the specification filed herewith
☒ application serial no., 09/398,934 filed September 1, 1999
☐ patent no., _____, issued _____

If the rights held by the above identified small business concern are not exclusive, each individual, concern or organization having rights to the invention is listed below* and no rights to the invention are held by any person, other than the inventor, who could not qualify as a small business concern under 37 CFR 1.9(d) or by any concern which would not qualify

as a small business concern under 37 CFR 1.9(d) or a nonprofit organization under CFR 1.9(e). *NOTE: Separate verified statements are required from each named person, concern or organization having rights to the invention averring to their status as small entities. (37 CFR 1.27).


NAME _____
ADDRESS _____
☐ INDIVIDUAL ☐ SMALL BUSINESS CONCERN ☐ NONPROFIT
ORGANIZATION

NAME _____
ADDRESS _____
☐ INDIVIDUAL ☐ SMALL BUSINESS CONCERN ☐ NONPROFIT
ORGANIZATION

I acknowledge the duty to file, in this application or patent, notification of any change in status resulting in loss of entitlement to small entity status prior to paying, or at the time of paying, the earliest of the issue fee or any maintenance fee due after the date on which status as a small entity is no longer appropriate. (37 CFR 1.28(b))

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application, any patent issuing thereon, or any patent to which this verified statement is directed.

NAME OF PERSON SIGNING Michael McGrane
TITLE OF PERSON OTHER THAN OWNER Vice President and General Counsel
ADDRESS OF PERSON SIGNING The Liposome Company, Inc., 1 Research Way,
Princeton Forrestal Center, Princeton, New Jersey 08540

SIGNATURE  DATE November 15, 1999

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Group Art Unit: 1502
Examiner: Gollamudi S. Kishore

In re PATENT REISSUE APPLICATION of:

Patentees : Patrick L. AHL et al.)

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For : REDUCTION OF LIPOSOME-INDUCED)
ADVERSE PHYSIOLOGICAL REACTIONS)

Attorney Docket :31839-150675)
TLC-201C-RIS)

**ASSENT OF ASSIGNEE
TO REISSUE**

Honorable Commissioner of Patents and Trademarks
Washington, D.C. 20231

Sir:

The undersigned states that she/he is empowered to execute this Assent on behalf of THE LIPOSOME COMPANY, INC., assignee of the entire interest in United States Patent No. 5,662,930 and hereby assents to the above-identified reissue application. An assignment from the inventors was recorded in the U.S. Patent and Trademark Office on August 12, 1994 at Reel 7097, Frame 0350-0353. The undersigned certifies that to the best of assignee's knowledge and belief, title is in the assignee seeking to take this action.

U.S. Patent No. 5,662,936, issued

I declare under penalty of perjury under the laws of the United States of America (28 U.S.C. § 1746 and M.P.E.P. 602) that the foregoing is true and correct.

Respectfully submitted,

THE LIPOSOME COMPANY, INC.



By: Michael McGrane

Title: Secretary and General Counsel

Date: September 1, 1999

MVS:rei
DC2-157402